IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC., Defendants.	C.A. No. 22-cv-228 (RGA) (JLH) (Consolidated)

DEFENDANTS' OPENING POST-TRIAL FINDINGS OF FACT

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TABLE OF ABBREVIATIONS

Term	Definition
'015 patent	U.S. Patent No. 11,098,015 (JTX-003)
'349 patent	U.S. Patent No. 11,298,349 (JTX-004)
'439 patent	U.S. Patent No. 11,091,439 (JTX-001)
'440 patent	U.S. Patent No. 11,091,440 (JTX-002)
1-1 impurity	6,7-dimethoxy-quinoline-4-ol
API	Active pharmaceutical ingredient
Berge	Berge et al., Pharmaceutical Salts, Journal of Pharmaceutical Sciences, 66, 1-19 (1977) (DTX-166)
Brown	International Publication No. WO 2010/083414 A1, to Brown et al. (DTX-291)
Bighley	Bighley et al., Salt Forms of Drugs and Absorption, in 13 Encyclopedia of Pharmaceutical Technology 453 (James Swarbrick & James C. Boylan eds., 1995) (DTX-167) ("Bighley" is a chapter in the "Swarbrick" encyclopedia)
Cabozantinib I Case	*Exelixis, Inc. v. MSN Lab'ys Priv. Ltd.*, No. CV 19-2017-RGA-SRF (D. Del.)
DTX	Defendants' Trial Exhibit
Exelixis	Plaintiff Exelixis, Inc.
FDA Guidance	FDA, Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Center for Drug Evaluation and Research (February 1987) (DTX-170)
FDA GTI Guidance	FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommend Approaches (DTX-091)
Gibson	Steele, Preformulation Predictions from Small Amounts of Compound as an Aid to Candidate Drug Selection, A Practical Guide from Candidate Drug Selection to Commercial Dosage Form (2001) (DTX-392)
Girindus	Girindus AG Kuensebeck
HCC	Hepatocellular carcinoma
HPLC	High-performance liquid chromatography
JTX	Joint Trial Exhibit
Lachman	Lachman et al., Pharmaceutical Dosage Forms, Second Edition, 1989 (PTX-553, which is a duplicate of DTX-288)

Term	Definition
Malate Salt Patents	Collectively, U.S. Patent Nos. 11,091,439; 11,091,440; and 11,098,015
MSN	MSN Laboratories and MSN Pharmaceuticals
MSN Laboratories	Defendant MSN Laboratories Private Limited
MSN Pharmaceuticals	Defendant MSN Pharmaceuticals Inc.
NCCN	National Comprehensive Cancer Network
POSA	Person of ordinary skill in the art
PTX	Plaintiff's Trial Exhibit
RCC	Renal cell carcinoma
Regis	Regis Technologies, Inc.
Remington's	Remington's Pharmaceutical Sciences Handbook (e.g., DTX-284)
Stahl	Stahl & Wermuth, "Monographs on Acids and Bases," in Handbook of Pharmaceutical Salts: Properties, Selection, and Use 10 (Stahl, P.H., Wermuth, C.G., eds., 2002) (PTX-610)
Swarbrick	Swarbrick et al., Encyclopedia of Pharmaceutical Technology (e.g., PTX-394)
Tong	Tong et al., In situ Salt Screening—A Useful Technique for Discovery Support and Preformulation Studies, Pharm. Dev. Technol. 3 (2), 215-223 (1998) (DTX-243)
TKI	Tyrosine kinase inhibitor
Vippagunta	Vippagunta et al., Crystalline solids, Advanced Drug Delivery Reviews, 48, 3-26 (2001) (DTX-191)

TABLE OF WITNESSES

Witness	Live or By Deposition	Description
Dr. Maureen Donovan	Live	Dr. Donovan is MSN's expert in the field of pharmaceutics, including solid-dose drug formulation. She testified regarding the noninfringement and invalidity of the formulation of claim 3 of the '349 patent.
Dr. Salvatore Lepore	Live	Dr. Lepore is MSN's expert in the field of chemistry. He testified regarding the obviousness of the asserted claim 3 of the '349 patent.
Dr. Jonathan Steed	Live	Dr. Steed is MSN's expert in the formation, characterization, and use of pharmaceutical salts. Dr. Steed testified regarding the invalidity under 35 U.S.C. § 112 and obviousness-type double patenting of the asserted claims of the Malate Salt Patents.
Dr. Anthony Mega	Live	Dr. Mega is MSN's expert in the field of medical oncology. He testified in response to Exelixis' assertions of long-felt, unmet need and clinical success.
Dr. Robert DeForest McDuff	Live	Dr. McDuff is MSN's expert in evaluating economics of the pharmaceutical industry. He testified in response to Exelixis' assertion of commercial success.
Dr. Jo Ann Wilson	By Deposition	Dr. Wilson is a named inventor of the '349 patent.
Dr. Peter Lamb	By Deposition	Dr. Lamb is a named inventor of the Malate Salt Patents.
Dr. Khalid Shah	Live	Dr. Shah is a corporate representative of Exelixis and a named inventor of the '349 patent.
Dr. David MacMillan	Live	Dr. MacMillan is Exelixis' expert in the field of organic and medicinal chemistry. He testified regarding expectation of success of recrystallization with respect to claim 3 of the '349 patent.
Dr. Bernhardt Trout	Live	Dr. Trout is Exelixis' expert in the field of pharmaceutical development and manufacturing, including with respect to crystallization of pharmaceutical salts. Dr. Trout testified as to the

Witness	Live or By Deposition	Description
		purported validity of the asserted claims of the Malate Salt Patents, particularly as to written description under 35 U.S.C. § 112 and obvious-type double patenting.
Dr. Allan Myerson	Live	Dr. Myerson is Exelixis' expert in the fields of separation and purification methods, crystallization, pharmaceutical formulation, and pharmaceutical manufacturing. Dr. Myerson testified regarding the purported nonobviousness of the '349 patent.
Dr. John Koleng	Live	Dr. Koleng is Exelixis' expert in pharmaceutical formulation. Dr. Koleng testified as to infringement of the asserted claim 3 of the '349 patent and purported nonobviousness of the Malate Salt Patents.
Dr. Daniel James George	Live	Dr. George is Exelixis' expert in the field of treatment of cancer, including renal cell carcinoma. He testified regarding purported clinical success, and long-felt, unmet need.
Michael Tate	Live	Mr. Tate is Exelixis' expert in the field of economic analysis as it pertains to commercial success. He testified regarding purported commercial success.

I. BACKGROUND

1. Exelixis[1] sued MSN for infringement of four patents. D.I. 124-1 ¶ 1.[2]

2. At trial, Exelixis asserted claim 4 of the '439 patent, which recites "[t]he [cabozantinib] malate salt according to claim 3, [which further depends from claim 1], wherein said salt is the (L)-malate salt." JTX-1.49.

3. At trial, Exelixis asserted claim 3 of the '440 patent, which recites "a pharmaceutical composition comprising the [cabozantinib] malate salt, wherein said salt is the (L)-malate salt or (D)-malate salt, and wherein said salt is crystalline; and a pharmaceutically acceptable excipient." JTX-2.49.

4. At trial, Exelixis asserted claim 2 of the '015 patent, which recites a "method of treating cancer, comprising administering to a subject in need thereof [cabozantinib] malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, said salt is crystalline, and said cancer is kidney cancer." JTX-3.49.

5. At trial, Exelixis asserted claim 3 of the '349 patent, which recites "[a] pharmaceutical composition for oral administration comprising [cabozantinib (L)-malate] one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition; and wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol." JTX-4.20. The code "1-1" is shorthand for "6,7-dimethoxy-quinoline-4-ol." Tr. 260:20–23.

6. The definition of a POSA applied by MSN's experts for the purposes of the asserted claims of the Malate Salt Patents is "[a] person who has a doctorate or a lesser graduate degree in

[1] All defined terms used therein are set forth in the Table of Abbreviations on page iv.
[2] Additional background information regarding the parties can be found at Joint Proposed Pretrial Order (D.I. 147) and Amended Exhibit 1 (D.I. 147), Uncontested Facts ¶¶ 1–5.

chemistry, pharmaceutical sciences, or a related discipline with 3 years or greater experience working with analytical techniques used to characterize forms of drug substances, and who has collaborated with others so that the team would collectively have had experience in synthesizing and analyzing complex small molecule compounds, or a physician with experience in the administration, dosing, and efficacy of drugs for the treatment of a particular disease state." *See, e.g.*, DDX(Steed)-5; Tr. 430:2–13.

7. The definition of a POSA applied by MSN's experts for the purposes of the asserted claim 3 of the '349 patent is "[a] person who had: A doctorate or a lesser graduate degree in pharmacy, chemistry, or a related discipline with 3 years or greater experience working in the research and development of formulations for the preparation of drug substances, and who has collaborated with others so that the team would collectively have had experience in synthesizing and analyzing complex small molecule compounds and impurities or degradation products of those compounds." *See, e.g.*, DDX(Donovan)-4; Tr. 187:24–188:11 (Donovan).

II. TECHNICAL BACKGROUND OF THE MALATE SALT PATENTS

A. Salt formation and salt screening were well-known techniques.

8. As of the priority date, approximately half of all drug products approved by the FDA included an API in salt form. Tr. 432:25–433:2 (Steed).

9. By 2009, salt screening was a known technique used to identify potential salt forms of a drug substance and was often outsourced to a contract resource organization and completed within a matter of weeks. Tr. 827:11–16 (Koleng), 433:15–22 (Steed).

10. Salt screening consists of four primary steps to identify and optimize the salt forms of a drug substance: (1) solubility tests, (2) selection of an acid or base counterion, (3) crystallization under a range of experimental conditions, and (4) characterization of residual solids. Tr. 433:9–14 (Steed); DDX(Steed)-8.

11. First, a POSA tests solubility in common solvents. Many solvents can be screened in a matter of minutes to observe the amount of API that dissolves. Tr. 433:23–434:14 (Steed).

12. Second, a POSA typically selects 15–20 potential counterions to test and assess compatibility with the free acid or base. Tr. 434:15–25 (Steed), 802:10–15 (Koleng).

13. The prior art identifying FDA-approved pharmaceutically acceptable acid counterions consistently listed around 50 acids, including malic acid. Tr. 435:6–24 (Steed); DDX(Steed)-9; DTX-177.3; DTX-167.4; DTX-166.2; PTX-610.336-337.

14. In selecting potential counterions, a POSA considers pK_a, which is an inherent property of a compound that indicates how strong its propensity is to form a salt. Tr. 436:15–21 (Steed). The pK_a of a compound and a counterion can be measured using a straightforward experimental technique called titration. Tr. 436:24–437:2 (Steed), 830:10–17 (Koleng).

15. Tong teaches that to form a salt, the "pK_a of the acid should be at least 2 pH units lower than the pK_a of the compound," which ensures that the acid is strong enough to transfer a hydrogen ion to the base, resulting in the formation of a salt. DTX-243.4; Tr. 437:3–12 (Steed). Dr. Trout agreed this "Rule of 2" was a "well-known rule of thumb." Tr. 931:20–25 (Trout).

16. Third, a POSA attempts to crystallize the salts that are formed from their acid-base choices under a range of experimental conditions. Tr. 437:18–438:7 (Steed). Most—but not all—salts formed in a screen are able to be crystallized. Tr. 438:8–14 (Steed).

17. Fourth, a POSA characterizes the physical properties of the solids formed by the salt screen, including crystalline structure (i.e., XRPD pattern), hygroscopicity, and melting point. Tr. 438:20–439:6 (Steed).

B. Crystalline polymorphs each have their own unique properties.

18. Solid salts are either crystalline or amorphous. Tr. 439:9–16 (Steed); DDX(Steed)-11. A crystalline salt has a regular repeating array of molecules that give rise to the crystal

structure. Tr. 439:9–16 (Steed). An amorphous salt does not have an underlying repeating regular arrangement, and the molecules are randomly arranged. Tr. 441:6–12 (Steed).

19. Crystalline salts may exist in multiple different polymorphic forms. Tr. 896:16–18 (Trout). Two different solid crystalline forms of the same compound will have a different repeating arrangement of molecules. Tr. 439:17–440:10 (Steed); DDX(Steed)-11. Different crystalline forms can arise from the different circumstances and conditions under which they are prepared. Tr. 440:23–441:5 (Steed), 907:5–8, 908:24–910:14, 921:16–22 (Trout).

20. Crystalline salts have a regular repeating underlying arrangement of molecules—a salt cannot be "crystalline" without being in a crystal form. Tr. 440:15–22, 560:13–19 (Steed).

21. The prior art reflects a strong preference (over 90%) for use of crystalline over amorphous forms of drugs. Tr. 441:19–23 (Steed).

22. Gibson teaches that "[a]ttempts to crystallize [an] amorphous [solid] should always be undertaken" because of problems associated with the physical and chemical stability of amorphous forms. DTX-392.0027; Tr. 442:5–21 (Steed).

23. Vippagunta teaches that "the occurrence of polymorphism is quite common among organic molecules" and "[c]rystalline polymorphs have the same chemical composition but different internal crystal structures and, therefore, possess different physico-chemical properties." DTX-191.0002. The different physico-chemical properties arise from differences in their underlying crystal structures. Tr. 443:2–15, 444:19–445:1 (Steed).

24. A POSA identifies the internal crystal structure of a compound using XRPD, which provides a unique "fingerprint" of a crystalline form. Tr. 898:8–10 (Trout), 443:16–444:5 (Steed); DTX-191.0018.

25. Intrinsic properties of a crystalline salt form include the crystal structure, melting

point, hygroscopicity, physical and chemical stability, solubility, dissolution rate, bioavailability, and processing characteristics. Tr. 444:19–447:8 (Steed); DDX(Steed)-13.

26. A POSA would expect each crystalline form of a compound to have its own set of properties, some of which might be similar to one another and others of which may be very distinct. Tr. 447:9–15 (Steed), 626:14–23 (Shah), 917:6–21 (Trout). For example, different crystal forms of a salt can have different densities, melting points, solubilities, hygroscopicity, stability, vapor pressure, and color. Tr. 918:17–919:17 (Trout).

27. FDA guidance states that "by the time of an NDA submission, the applicant should have established whether (or not) the drug substance exists in multiple solid-state forms" (e.g., crystalline forms). DTX-170.35; Tr. 448:5–11 (Steed), 627:25–628:17 (Shah). This is important because each crystalline form will have different pharmaceutical properties like dissolution and bioavailability. Tr. 448:5–17 (Steed), 896:19–897:4, 923:20–23 (Trout).

28. To determine whether a salt exists in multiple crystalline forms, prior-art methods existed, such as polymorph screening, that crystallized the salt under a representative range of conditions to identify whether various crystalline forms would result. Tr. 449:5–15 (Steed).

29. As of the priority date, drugs under development were essentially always subjected to crystalline polymorph screening. Tr. 449:16–450:16 (Steed), 923:7–23 (Trout).

30. Prior-art cautionary tales like Norvir show that one polymorph of an API may be pharmaceutically acceptable while another polymorph is not. Tr. 924:5–9, 924:20–925:5 (Trout).

III. INSUFFICIENT WRITTEN DESCRIPTION OF THE MALATE SALT PATENTS

A. Exelixis did not possess all crystalline cabozantinib (L)-malate salts.

31. All crystalline cabozantinib (L)-malate salts fall within the scope of the Malate Salt Patents' asserted claims. Tr. 558:1–6 (Steed).

32. Dr. Trout agreed that the asserted claims of the Malate Salt Patents cover the

crystalline cabozantinib (L)-malate salt forms known to exist, including at least Forms N-1 and N-2 and MSN's Form S. Tr. 901:8–22 (Trout). Dr. Trout also agreed that if the asserted claims of the Malate Salt Patents used the phrase "[w]herein said salt is a crystalline form," the claims would cover the crystalline cabozantinib (L)-malate forms known to exist, including at least Forms N-1 and N-2 and MSN's Form S. Tr. 900:16–901:7 (Trout).

33. The asserted claims are not limited to the most "pharmaceutically relevant" or "thermodynamically stable" crystalline cabozantinib (L)-malate salts. Tr. 559:18–560:6 (Steed).

34. The relevant genus for determining whether the asserted claims lack sufficient written description is "any crystalline cabozantinib (L)-malate salt." Tr. 451:13–16 (Steed).

35. There are 11 known crystalline cabozantinib (L)-malate salts, but the genus is potentially infinite because others could be discovered in the future. Tr. 451:17–21 (Steed).

36. Exelixis possessed and disclosed two closely related forms of crystalline cabozantinib (L)-malate (N-1 and N-2). Tr. 451:22–452:1 (Steed), 625:13–16, 632:20-25 (Shah).

37. The specification contains detailed characterization data for crystalline Forms N-1 and N-2, including XRPD, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and moisture sorption data. Tr. 452:10–453:18 (Steed), 902:19–904:2 (Trout); JTX-0001.0007, 11–14, 18–20.

38. Exelixis reported in its NDA submission to the FDA that "[c]abozantinib ([L])-malate was found to exist in two neat, closely related, crystalline forms (N-1 and N-2) that have similar properties," and that "[n]o other forms were identified." DTX-0020.0002; Tr. 455:5–13 (Steed), 627:14–17, 629:8–630:11 (Shah).

39. U.S. Patent Nos. 9,809,549 and 8,877,776, which issued before the Malate Salt Patents, claim crystalline Forms N-1 and N-2 of cabozantinib (L)-malate, respectively. JTX-

0009.0012, .0047; JTX-0010.0004, .0047; Tr. 453:19–454:11 (Steed); DDX(Steed)-18.

40. Patents issued and patent applications published before the applications from which the Malate Salt Patents issued report 11 different crystalline forms of cabozantinib (L)-malate, identified as N-1 and N-2 (Exelixis); S (MSN); M1, M2, M3, and M4 (Mylan); and C2, C3, C4, and C5 (Cipla). JTX-0009.35; DTX-333.01; PTX-256.01; DTX-222.01; DTX-121.05-.06; Tr. 455:23–456:12 (Steed).

41. XRPD diffractograms characterizing the crystal structure for each of the 11 reported crystalline forms of cabozantinib (L)-malate are disclosed in the patent literature. JTX-0009.05, .12; DTX-333.02–.04; PTX-256.02, .05, .08, .09; DTX-222.0028, 31, 34–35; DTX-121.0029–31; Tr. 455:23–456:12 (Steed).

42. The XRPD diffractograms for the 11 reported crystalline forms confirm that they are each distinct and unique. Tr. 456:15–458:4, 560:20–561:19 (Steed); DDX(Steed)-20.

43. It is normal and not surprising that when comparing XRPD diffractograms for different crystalline forms, there are sometimes overlapping peaks, but the overall patterns are distinct. Tr. 457:10–22 (Steed).

44. Preparation methods for making each of the 11 reported crystalline forms of cabozantinib (L)-malate are disclosed in the patent literature. JTX-0009.40–.43; DTX-333.0014–18; PTX-256.24–.26; DTX-222.0019–23; DTX-121.0018–22; Tr. 458:5–9 (Steed).

45. Each of the 11 reported crystalline forms of cabozantinib (L)-malate are prepared in different ways, which leads to their different forms. DDX(Steed)-21; Tr. 458:10–460:3 (Steed), 911:22–912:6 (Trout).

46. At the priority date, based on the teachings of the prior art, a POSA would have had a strong reason to expect that crystalline forms of cabozantinib (L)-malate other than Form N-1

and N-2 existed. Tr. 460:11–20 (Steed).

47. The Malate Salt Patent inventors did not invent any crystalline form of cabozantinib (L)-malate other than Forms N-1 and N-2. Tr. 902:11–18 (Trout).

48. There is no description or working examples in the specification of any crystalline form of cabozantinib (L)-malate other than Forms N-1 and N-2. Tr. 904:13–15, 904:19–23 (Trout).

49. A POSA would not know whether other crystalline forms of cabozantinib (L)-malate existed based on the disclosures in the Malate Salt Patents. Tr. 905:3–8 (Trout).

50. There is nothing in the Malate Salt Patents that enables a POSA to predict whether there would be other forms of crystalline cabozantinib (L)-malate. Tr. 905:9–12 (Trout).

51. There is no way a POSA can predict what polymorph might be obtained without conducting testing. Tr. 906:3–11 (Trout).

B. Forms N-1 and N-2 are not representative species of the genus of crystalline cabozantinib (L)-malate salts.

52. Different crystalline cabozantinib (L)-malate salts do not have—and would not be expected by a POSA to have—the same crystalline structure, physical properties, chemical properties, or functional properties. Tr. 462:13–19, 559:4–12 (Steed).

53. The crystalline structure of Forms N-1 and N-2 are not representative of the crystalline structure of other crystalline cabozantinib (L)-malate salts that exist or that could reasonably be expected by a POSA to exist. Tr. 460:21–461:9 (Steed).

54. The properties of Forms N-1 and N-2 are not representative of the properties of other crystalline cabozantinib (L)-malate salts that exist or that could reasonably be expected by a POSA to exist. Tr. 466:1–14 (Steed).

55. The Malate Salt Patent specification reports that crystalline cabozantinib (L)-malate Forms N-1 and N-2 have improved properties over the cabozantinib freebase and other salts

of cabozantinib. JTX-0001.0036–.37; Tr. 461:14–462:12 (Steed).

56. The melting points of Form N-1 and N-2 are 187°C and 186°C, respectively. JTX-0001.0049; Tr. 463:3–6 (Steed). Mylan's Form M-4 has a melting point of 174.87°C and MSN's Form S has a melting point of 113°C. DTX-222.36; Tr. 463:12–20 (Steed).

57. A POSA would not expect other forms of crystalline cabozantinib (L)-malate to have the same melting point as Forms N-1 or N-2. Tr. 463:7–11 (Steed).

58. Forms N-1 and N-2 are non-solvated forms of crystalline cabozantinib (L)-malate that are stable (show no solvent loss) up to 185°C in a TGA experiment. JTX-0001.0037; Tr. 463:25–464:6 (Steed). Mylan's Form M-1 is a solvated crystalline form that shows 4.26% solvent loss in a TGA experiment. DTX-222.30; Tr. 464:15–23 (Steed). MSN's From S is a hydrated crystalline form (i.e., a solvated form where the solvent is water). Tr. 562:8–11 (Steed).

59. A POSA would not expect other forms of crystalline cabozantinib (L)-malate to show no solvent loss in a TGA experiment as Forms N-1 or N-2 do. Tr. 464:8–14 (Steed).

60. Forms N-1 and N-2 are non-hygroscopic, while MSN's Form S is hygroscopic. JTX-0001.0037; Tr. 464:24–465:15 (Steed), 925:9–17 (Trout).

61. A POSA would not expect other forms of crystalline cabozantinib (L)-malate salts to have the same non-hygroscopicity as Forms N-1 or N-2. Tr. 465:11–15 (Steed).

62. A POSA would not expect other forms of crystalline cabozantinib (L)-malate to have the same solubility as Form N-1 or N-2. JTX-0001.0037; Tr. 465:16–25 (Steed).

63. It is important to identify and isolate different polymorphs of a crystalline salt, Tr. 896:19–22 (Trout), because significant differences in chemical and physical characteristics may arise with changes in crystalline form, Tr. 896:23–897:1 (Trout), that may affect the manufacturability, performance, and quality of a drug product. Tr. 897:2–4 (Trout).

64. The range and combinations of crystal growth structures are virtually infinite, and there is no way to guarantee the preparation of additional polymorphs of a substance, much less the generation of all of them. Tr. 922:10–17 (Trout).

IV. OBVIOUSNESS-TYPE DOUBLE PATENTING OF THE MALATE SALT PATENTS

A. Claim 5 of the '473 patent is a double-patenting reference claim.

65. U.S. Patent No. 7,579,473 ("the '473 patent") issued on August 25, 2009, and is assigned to Exelixis. DTX-0013; Tr. 468:6–11 (Steed). It expires in 2026. Tr. 468:23–24 (Steed).

66. The cabozantinib molecule is identified by structure in claim 5 of the '473 patent, and by name in the Malate Salt Patents. DTX-0013.0207; JTX-001.02; JTX-002.02; JTX-003.02; Tr. 469:13–17 (Steed), 469:13–17 (Steed). Claim 5 also covers "pharmaceutically acceptable salts [of cabozantinib]." JTX-0013.0207.

67. Crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. Tr. 469:24–470:1 (Steed), 831:9–12 (Koleng), 926:21–927:9 (Trout).

68. The genus of pharmaceutically acceptable salts claimed in the '473 patent includes the species of crystalline (L)-malate salts claimed in the Malate Salt Patents. Tr. 470:2–6 (Steed).

B. Preparation of the crystalline (L)-malate salt of cabozantinib in a salt screen would have been obvious.

69. A POSA would have been motivated to prepare the crystalline (L)-malate salt of cabozantinib in a routine salt screen with a reasonable expectation of success. Tr. 470:7–18, 478:19–479:5 (Steed); DDX(Steed)-25. There is nothing in the prior art that would teach away from a POSA's preparing the crystalline (L)-malate salt of cabozantinib. Tr. 479:2–5 (Steed).

70. There is nothing about the cabozantinib molecule that would have made the salt screen experiments specifically complex. Tr. 621:2–16 (Shah).

71. A POSA would have reviewed the prior art to identify counterions that were

previously used in FDA-approved drugs, and (L)-malic acid was identified in prior-art lists. Tr. 470:19–471:3 (Steed); DTX-177.3; DTX-167.4; DTX-166.2; PTX-610.336-337.

72. Sunitinib was an FDA-approved TKI formulated as an (L)-malate salt in the prior art that would indicate that (L)-malic acid is a suitable acid for TKIs. Tr. 471:8–14 (Steed).

73. A POSA would look to use safe, nontoxic acids as counterions, Tr. 71:15–19 (Steed), and the prior art reported that malic acid is nontoxic and a natural product that comes from fruits and is sometimes called apple acid. Tr. 471:20–23 (Steed).

74. Bighley identifies 12 potential nontoxic organic acids, including malic acid, that can be used to avoid issues that can be encountered with mineral acid salts. DTX-167.0036; Tr. 472:16–473:1, 473:6–8, 472:16–473:1, 473:6–8, 554:2–555:1 (Steed).

75. Bighley reports that the besylate salt had been used in 0.26% of salt forms that had been clinically evaluated in humans or were commercially marketed through 1993, totaling four times. DTX-167.3-4; Tr. 553:10–23 (Steed); PDX-9.3.

76. A POSA would have known and taken into account Tong's "Rule of 2" when selecting counterions for salt screening. Tr. 932:14–933:1 (Trout).

77. Dr. Shah was aware of Tong's Rule of 2 as of the mid-2000s. Tr. 623:9–12 (Shah). Dr. Koleng was aware—and a POSA would also have been aware—of the principle of using pK_a to select salts for a salt screen as of 2009. Tr. 830:1–9 (Koleng).

78. Pharmorphix selected acids for their own cabozantinib salt screen based on a measure of pK_a and Tong's "Rule of 2" guidance, not "Rule of 3" guidance. Tr. 622:18–21, 624:6–9 (Shah); PTX-87.03.

79. The pK_a of cabozantinib is not reported in the prior art but could be readily measured by titration. Tr. 473:13–14 (Steed), 830:10–13 (Koleng).

80. The pK_a of malic acid was reported in the prior art as ~3.4. Tr. 473:15–17 (Steed).

81. Stahl teaches that "[t]he comprehensive reviews on pharmaceutical salts by *Berge, Bighley*, and *Monkhouse* are frequently referred to when the formation of salts of a[] new chemical entity is considered" but "[a]ccumulated knowledge and experience has led to a reduction of the number of acids and bases regarded as innocuous," leading to "a revised list of useful salt-forming acids and bases" presented by Stahl. PTX-610.333.

82. Stahl teaches that "some substances may be considered unobjectionable because they are used profusely in food processing" and "in the USA, the FDA grants the GRAS (= 'Generally Regarded As Safe') status to food additives and processing aids." PTX-610.334; Tr. 836:24–837:4 (Koleng).

83. GRAS status is a desirable property when selecting a counterion. Tr. 475:14–476:1 (Steed). Dr. Koleng agreed that acids may be unobjectionable for how they are used in a salt screen based on their GRAS status. Tr. 837:15–21 (Koleng).

84. There is a relatively limited list of previously used pharmaceutically acceptable counterions that would meet Tong's Rule of 2 for cabozantinib and were recognized as safe, Tr. 476:15–21 (Steed), and that list could be easily encompassed by a routine and customary salt screen. Tr. 476:19–21 (Steed). For example, Stahl's list of potential acid counterions lists nine acids, including malic acid, that meet the Tong "Rule of 2" for cabozantinib and are identified as GRAS. PTX-610.336-.337; Tr. 476:2–9 (Steed), 831:6–8, 837:22–25 (Koleng).

85. A POSA would also consider the structural compatibility of malic acid and cabozantinib when selecting acids for a salt screen. Tr. 476:24–477:25 (Steed). A POSA would have concluded that cabozantinib and (L)-malic acid would be likely to form a stable crystal. Tr. 478:1–5 (Steed); DDX(Steed)-26.

86. Following the routine and customary path of a salt screen, a POSA would have arrived at cabozantinib (L)-malate and been able to analyze its properties. Tr. 478:9–18 (Steed).

87. Crystalline salt forms have desirable properties over amorphous salt forms, including greater stability and less hygroscopicity, and thus a POSA would be motivated to prepare a crystalline form of cabozantinib (L)-malate. Tr. 478:19–479:1 (Steed).

88. It took 30 minutes to an hour for Peter Lamb, Exelixis' Executive Vice President of Scientific Strategy and named inventor of the Malate Salt Patents, to evaluate the results of Pharmorphix's salt screen and select (L)-malate salt as the salt with the most desirable properties. Tr. 580:1–24 (Lamb); PTX-87.

C. Using crystalline cabozantinib (L)-malate in a pharmaceutical composition to treat kidney cancer would have been obvious to a POSA.

89. U.S. Patent Publication No. 2007/0054928 ("the '928 application"), which ultimately issued as the '473 patent, is prior art to the Malate Salt Patents. Tr. 480:1–3 (Steed), DTX-180.

90. The '928 application teaches administration of the compounds of the invention, including cabozantinib, or their pharmaceutically acceptable salts. Tr. 480:15–481:6 (Steed); DTX-180.145, .314, .317.

91. The '928 application and '440 patent do not identify any specific pharmaceutical compositions containing cabozantinib (L)-malate or how to make them. Tr. 481:7–11 (Steed).

92. A POSA would have found obvious and been motivated to prepare a pharmaceutical composition of crystalline cabozantinib (L)-malate salt. Tr. 481:12–20 (Steed).

93. The '928 application teaches the use of cabozantinib to treat kidney cancer. Tr. 482:9–483:3 (Steed); DTX-180.04–.05, .143.

94. The '928 application, like the '015 patent, does not identify any specific methods

or properties of kidney cancer treatment resulting from administering cabozantinib (L)-malate, such as permeability or bioavailability. Tr. 483:4–9, 556:20–24 (Steed).

95. A POSA would have found obvious and been motivated to use crystalline cabozantinib (L)-malate salt to treat kidney cancer. Tr. 483:10–20 (Steed).

V. TECHNICAL BACKGROUND OF THE '349 PATENT

A. Drug substances and drug products were known to contain impurities.

96. The FDA requires "the reporting and control" of "the actual and potential impurities most likely to arise during the synthesis, purification, and storage" of a drug substance. Tr. 756:16–757:21 (Myerson).

97. Impurities may arise from three general classes—starting materials (e.g., reagents or intermediates), degradation products, or side-products/byproducts generated by the synthetic process. Tr. 690:7–13 (Myerson); *see also* DTX-328.1; Tr. 657:18–658:1 (MacMillan).

98. Starting-material impurities arise when residual starting material not consumed in the reaction carries through to the final product. Tr. 690:14–691:2 (Myerson); DTX-328.1.

99. Degradation-product impurities arise when the desired molecule degrades by undergoing a chemical change. Tr. 658:2–8 (MacMillan), 691:7–9 (Myerson).

100. Side-product/byproduct impurities arise when the reaction produces an unwanted product. Tr. 657:18–658:1 (MacMillan), 691:3–6 (Myerson).

101. Impurities can be quantified and monitored using common analytical techniques such as chromatography (e.g., HPLC). DTX-291.24–25 ¶ 97; Tr. 263:20–264:2, 269:22–270:3 (Lepore), 758:13:23 (Myerson).

B. FDA required the identification and control of GTIs.

102. Genotoxic impurities ("GTIs") are of increased concern because they are unusually toxic. DTX-328.1; Tr. 265:14–21 (Lepore), 765:1-12 (Myerson).

103. Whether an impurity is genotoxic would have been "easily demonstrated" by a simple two-step assessment. DTX-328.1; Tr. 266:3–8 (Lepore).

104. First, impurities were screened for potential genotoxicity based on whether the impurity raises a "structural alert." DTX-091.9 ("FDA GTI Guidance"); Tr. 303:3-10 (Lepore), 766:13–767:25 (Myerson).

105. Second, an impurity with a structural alert would "always" have been further tested using an in vitro mutation assay—i.e., the "Ames" test—to determine whether it is genotoxic. DTX-091.9; DTX-328.1; Tr. 266:3–8, 303:3–15 (Lepore), 768:1–4 (Myerson).

106. The FDA recommended that "manufacturers should strive to achieve the lowest levels of [GTIs] that are technically feasible" because "[e]xposure to even low levels of these impurities may be of significant concern." DTX-091.5–6; Tr. 302:9–18(Lepore).

107. U.S. and European regulatory authorities required the control of GTIs at low PPM levels in drug substances. DTX-328.1; Tr. 266:9-19 (Lepore).

108. Starting materials were known sources of GTIs. DTX-328.1; Tr. 264:23–265:6 (Lepore). FDA GTI Guidance "applie[d] to known starting materials." DTX-091.4; Tr. 302:1–7 (Lepore).

109. In accordance with FDA Guidance, Exelixis assessed "all starting materials … and potential impurities" for "structural alerts" and then further evaluated those materials with structural alerts in mutagenicity assays for genotoxicity. Tr. 570:4–17 (Wilson).

110. To use a drug substance in a clinical trial, the FDA provided acceptable daily intake levels of GTIs. DTX-091.13–14. To meet these daily intake levels under the circumstances would require levels below 50 ppm. Tr. 307:3–19 (Lepore).

C. Quinoline and quinoline analogs were known to be genotoxic.

111. "[T]here were a lot of examples in the literature of quinoline compounds being

mutagenic." Tr. 575:8–13 (Wilson). An EPA toxicological review concluded that quinoline is genotoxic. DTX-272.30; Tr. 304:1–8 (Lepore). A study of quinoline analogs concluded that the majority (12 of 17 analogs) were genotoxic. DTX-313.1, .4; Tr. 304:17–305:13 (Lepore).

112. If a compound is a quinoline, that would have raised a structural alert. Tr. 304:9–16 (Lepore), 770:5–11 (Myerson).

D. Recrystallization was known and widely used as a GTI control strategy.

113. Recrystallization was a "conventional" and "highly effective method of purifying a solid substance." DTX-251.4; Tr. 308:17–25, 310:8–311:3 (Lepore), 792:23–793:18 (Myerson).

114. Recrystallization was a known method to reduce the presence of GTIs in an API. DTX-328.9; Tr. 310:11–21 (Lepore), 572:8–573:5, 575:4–7 (Wilson).

115. FDA GTI Guidance recommended changing purification routes, which would include adding recrystallization, to "maximize the removal of the relevant impurity." DTX-091.5; Tr 309:4–14 (Lepore), 792:23–25 (Myerson).

116. FDA Guidance on manufacturing APIs recommended using recrystallization to "reprocess" a batch if too much of an impurity is present. DTX-304.43; Tr. 309:15–310:3 (Lepore).

117. Many prior-art examples successfully used recrystallization to purify an API of an impurity, including minimizing GTIs to less than 1 ppm. DTX-328.9; Tr. 310:8–21 (Lepore).

E. Synthesis of pure cabozantinib (L)-malate and its formulations were known.

118. Brown is an Exelixis international patent publication published on July 22, 2010, and is prior art to the '349 patent under 35 U.S.C. § 102(a). DTX-291; Tr. 267:2–12 (Lepore).

119. Brown Example 1 discloses a synthetic route and stepwise narrative description for synthesizing cabozantinib (L)-malate. DTX-291.25–28; Tr. 267:13–268:10 (Lepore).

120. Brown discloses that cabozantinib (L)-malate can be "substantially pure," which can be "about 100%" pure. DTX-291.24 ¶ 97; Tr. 269:5–16 (Lepore).

121. Brown discloses that if cabozantinib (L)-malate is not 100% pure, it may contain chemical impurities, such as processing or reaction impurities, which can be identified using analytical techniques like chromatography (e.g., HPLC). DTX-291.24-25 ¶ 97; Tr. 269:17–270:3, 361:23–362:13 (Lepore).

122. Brown discloses that the "particularly preferred" dosage form for cabozantinib (L)-malate is oral capsules or tablets. DTX-291.22 ¶ 87; Tr. 372:2–11; 390:25–391:8 (Donovan).

123. Brown discloses that cabozantinib (L)-malate can be formulated by methods known in the art, including as described in Remington's (DTX-291.21 ¶ 82; Tr. 372:20–373:5 (Donovan)), and can be mixed with fillers, disintegrants, lubricants, and talc, a well-known glidant. DTX-291.21 ¶ 82; Tr. 373:10–17; 392:12–20 (Donovan).

F. Fillers, disintegrants, glidants, and lubricants were commonly used together in tablet and capsule formulations.

124. Drugs are most frequently administered "orally by means of solid dosage forms such as tablets and capsules." DTX-284.4; Tr. 374:16–375:3 (Donovan).

125. Remington's and Lachman[3] disclose that common tablet ingredients include diluents (i.e., fillers), glidants, lubricants, and disintegrants, and both references disclose descriptions and examples of each of those classes of excipients. DTX-284.6–.8; Tr. 375:4–20 (Donovan); PTX-553.113, .128, .131, .135; Tr. 377:13–378:1 (Donovan).

126. Lachman further discloses that these four classes of excipients can be used together in wet granulation. PTX-553.171; Tr. 378:21–379:3 (Donovan).

127. Lachman provides drug-agnostic prototype formulations, which are suitable for many drug substances, that comprise a filler, disintegrant, glidant, and lubricant PTX-553.176–.177, .188; Tr. 379:4–380:19 (Donovan) (discussing DTX-288, which is a duplicate of PTX-553).

[3] Dr. Donovan's testimony referred to Lachman as DTX-288, which is a duplicate of PTX-553.

128. The ’081 Application discloses that TKIs can be formulated into tablets and capsules for oral administration comprising a filler, disintegrant, lubricant, and glidant. DTX-335.14–15; Tr. 381:16–383:4; 394:9-13 (Donovan).

129. A POSA would have known that talc can be used as a glidant. DTX-284.8; Tr. 376:5–16; 383:2-4 (Donovan); *see also* DTX-335.15; Tr. 173:1–6 (Koleng).

G. Formulators knew how to limit impurities in a drug product.

130. FDA GTI Guidance requires identification and control of GTIs during formulation of drug products. DTX-091.5; Tr. 386:17–387:6 (Donovan); 264:23-265:25 (Lepore); DTX-238.1.

131. “In designing a solid dosage form it is necessary … to know that no toxic substances are formed.” PTX-553.63; Tr. 385:1–7 (Donovan) (discussing DTX-288, which is a duplicate of PTX-553)..

132. It was well known, and “a tenet of formulation,” to limit impurities when formulating drug compositions. Tr. 396:10–16 (Donovan).

133. To prevent degradation impurities during formulation, chemical stability is evaluated during preformulation studies. DTX-325.14; Tr. 386:2–13 (Donovan).

134. Preformulation studies include excipient-compatibility studies to identify which excipients are physically and chemically compatible with the drug substance. DTX-288.98–.99; 385:8–20 (Donovan).

VI. OBVIOUSNESS OF CLAIM 3 OF THE ’349 PATENT

A. Brown Example 1 inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity.

135. If a POSA faithfully follows Brown Example 1, as Regis did, the POSA would necessarily and inherently obtain cabozantinib (L)-malate that is essentially free of the 1-1 impurity. Tr. 299:10–18; 366:14–18 (Lepore).

1. Expert testimony confirms that Brown Example 1 inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity.

136. Dr. Lepore explained that Brown Example 1's synthetic scheme and narrative description discloses in a stepwise fashion "[e]verything" that is needed to synthesize cabozantinib (L)-malate. DTX-291.25–28; Tr. 266:233–268:6 (Lepore).

137. Dr. Lepore compared the synthetic schemes and narrative description from Brown Example 1 to the synthetic scheme and narrative description used to manufacture the Regis Batches, and concluded they were the same. Tr. 271:20–275:21, 364:3-365:13 (Lepore).

138. Dr. Myerson testified that there is "always variability in a synthetic process," including in the B-2 process described in the '349 patent (Tr. 786:24–787:7); however, Dr. Shah testified that such a variable process can nevertheless be "a consistent reproducible manufacturing process" with controls in place to synthesize cabozantinib (L)-malate that is essentially free of the 1-1 impurity. Tr. 615:9–616:10 (Shah).

139. Drs. Lepore, MacMillan, and Myerson testified that there are three routes by which the 1-1 impurity could become present in cabozantinib (L)-malate API—due to the 1-1 starting material that carries through to the final API, due to the formation of the impurity as a degradation product, or due to the formation of the impurity as a byproduct. Tr. 690:7–13 (Myerson), 657:18–658:1 (MacMillan), 264:23–265:6 (Lepore) (discussing DTX-328.1 ("[I]mpurity compounds … aris[e] as residues of starting materials, reagents, intermediates, or as side-products generated by the synthetic processes or degradation reactions.")).

140. Brown Example 1 inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity, because no 1-1 starting material carries through to the cabozantinib (L)-malate product, no degradation causes formation of the 1-1 impurity, and no byproducts lead to the 1-1 impurity. Tr. 668:16–669:14 (MacMillan admitting that a POSA "would not believe there would

be any [1-1] … ending up" in the cabozantinib (L)-malate), 663:8–11 (MacMillan admitting that a POSA "would not expect [degradation] to happen").

141. **Starting Material.** Drs. MacMillan and Myerson testified that the 1-1 starting material used in Brown Example 1 would not carry through to the cabozantinib (L)-malate API. Tr. 668:16–669:14, 677:11–25 (MacMillan), 721:10–25 (Myerson) ("By the time you make cabozantinib (L)-malate, you would expect very small amounts, if any, detectable 1-1 impurity.").

142. Each of the five steps of the Brown Example 1 process includes its own purification process (or workup step) that would purge the 1-1 impurity. Tr. 332:24–333:1 (Lepore); 677:20–25, 678:14–680:1, (MacMillan); 690:14–691:15 (Myerson).

143. Step 1 of the Brown Example 1 process requires that less than 2% of the 1-1 starting material be remaining from the reaction prior to proceeding with the step 1 purification. Tr. 665:20–666:17 (MacMillan), 708:23–709:14 (Myerson).

144. The step 1 purification of Brown Example 1 includes a crystallization, which would "further reduce the 1-1 impurity level" and leave only "a very small amount" of the 1-1 impurity at the end of step 1. Tr. 295:14–296:11 (Lepore), 666:18–667:9, 679:6–22 (MacMillan).

145. Any 1-1 starting material remaining after step 1 "would be purged" in the subsequent purifications of the Brown Example 1 process. Tr. 679:23–680:1; *see also* 667:12–668:1, 668:16–669:9 (MacMillan), 708:23–709:14 (Myerson).

146. Other reagents used in subsequent steps could react with the 1-1 impurity to remove, or purge, the 1-1 impurity. Tr. 668:16–669:6, 677:20–25 (MacMillan).

147. "[B]y the end of the fifth step" of the Brown Example 1 process, any 1-1 present would be "purged." Tr. 679:23–680:1 (MacMillan), 708:23–709:14 (Myerson).

148. **Degradation Product.** Drs. MacMillan and Myerson testified that the 1-1 impurity

would not be expected to form by degradation during the Brown Example 1 process. Tr. 663:8–11 (MacMillan), 709:15–19 (Myerson).

149. The 1-1 impurity would not form as a degradation product because the relevant functional group that would need to degrade is "very stable." Tr. 661:1–18 (MacMillan).

150. A POSA "would not expect" the 1-1 impurity to form by degradation by hydrolysis in Brown Example 1. Tr. 661:1–18 (MacMillan).

151. Cabozantinib salt formation in Brown Example 1 makes the compound even more stable and less likely to undergo hydrolysis. Tr. 661:25–662:15 (MacMillan).

152. The addition of malic acid would not catalyze the formation of the 1-1 impurity. Tr. 662:16–25 (MacMillan).

153. **Byproduct.** The 1-1 impurity is not a byproduct of any reaction in the Brown Example 1 process. DTX-291.25 Scheme 1; Tr. 656:12-18 (MacMillan) ("[A] POSA would not have expected the 1-1 impurity to have formed as a result of the Brown process.").

154. While none of the three mechanisms will lead to levels above 200 ppm of the 1-1 impurity, cabozantinib (L)-malate produced by Brown Example 1 will comprise some nonzero amount of the 1-1 impurity. Tr. 680:2–10 (MacMillan); 709:5-14 (Myerson).

2. All relevant data confirms that Brown Example 1 inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity.

155. Regis manufactured three batches of cabozantinib (L)-malate between 2005 and 2007 for use in clinical studies. DTX-080.2; DTX-038.8; Tr. 270:21–271:1, 277:19–21 (Lepore).

156. Regis used the Brown Example 1 process. *Compare* DTX-038.9–.12, *with* DTX-291.25–.28; Tr. 270:21–23, 364:3–13 (Lepore), 786:2–7 (Myerson: "The language used by Exelixis in its IND to describe how the clinical material was manufactured [by Regis] is identical to Example 1 Brown.").

157. Exelixis communicated to FDA the details of the Regis Process, and those details are identical to Brown Example 1. DTX-038.9–12; Tr. 336.11–16 (Lepore), 786:2–7 (Myerson).

158. The word "approximately," which appears in the narrative description of the Brown Example 1 process, is used "all the time" in synthetic processes when describing parameters that do not have to be precise. Tr. 787:24–788:16 (Myerson).

159. It is undisputed that the Regis Batches followed the Brown Example 1 process within the allowed variability. Tr. 365:9–366:1 (Lepore), 785:21–786:1 (Myerson).

160. Exelixis analyzed the presence of the 1-1 impurity in the Regis Batches using three different analytical methods, each of which confirmed that the Regis Batches were essentially free of the 1-1 impurity. Tr. 276:5–17 (Lepore), 718:15–19 (Myerson).

161. Using the AMRI HPLC Method, which has a limit of detection of 200 ppm, Exelixis reported to FDA that no 1-1 impurity was detected in the Regis Batches. DTX-080.2; DTX-125.11; Tr. 279:4–280:7 (Lepore). Using the Exelixis HPLC Method, which has a limit of detection of 200 ppm, Exelixis reported that no 1-1 impurity was detected in the Regis Batches. PTX-098.15–.17, .19; Tr. 281:14–17, 282:13–283:6 (Lepore). Using the GTI HPLC and LC/MS methods, which have a limit of detection of 1 ppm, Exelixis reported that the Regis Batches were always less than 50 ppm. DTX-130.8; DTX-128.72; Tr. 286:2–287:24 (Lepore).

162. The Regis Batches of API were manufactured into capsules that were essentially free of the 1-1 impurity. PTX-009.20, .22–.23; PTX-068.86; Tr. 289:2–17, 292:2–6 (Lepore).

3. Girindus deviated from the Brown Example 1 process.

163. Girindus did not use the Brown Example 1 process when manufacturing its single batch of cabozantinib (L)-malate. Tr. 293:24–294:1, 299:4–9 (Lepore).

164. Girindus committed more than six deviations and a manufacturing error from Brown Example 1. DTX-062.14–.25; DDX(Lepore)-30; 295:2–5 (Lepore); 791:5–23 (Myerson).

165. A deviation fundamentally changes the synthetic process. Tr. 295:6–10 (Lepore).

166. One deviation occurred when Girindus failed to perform the crystallization purification in step 1 of Brown Example 1. *Compare* DTX-291.26, *with* DTX-062.7; Tr. 295:14–296:11 (Lepore). Drs. MacMillan and Lepore testified that this step would have "reduce[d] the 1-1 impurity level." Tr. 295:14–296:11 (Lepore); 666:18–667:9, 679:6–22 (MacMillan).

167. Another deviation occurred when Girindus added an additional step to the synthetic scheme, thereby producing a new intermediate—an aminal major impurity—instead of producing the desired 1-4 intermediate. DTX-062.14; Tr. 296:15–298:20 (Lepore).

168. Other deviations occurred when Girindus exposed the compound to heat, water, and acid, and left the material standing exposed to those conditions over a weekend—conditions that are not described in Brown Example 1. Tr. 298:11–399:9 (Lepore).

B. It would have been obvious to a POSA to produce cabozantinib (L)-malate essentially free of the 1-1 impurity.

169. If the Brown Example 1 process produced cabozantinib (L)-malate that was not essentially free of the 1-1 impurity, a POSA would have found it obvious to obtain cabozantinib (L)-malate that was essentially free of the 1-1 impurity. Tr. 299:23–300:4 (Lepore).

1. FDA Guidance requiring the industry to identify GTIs would have motivated a POSA to identify the 1-1 impurity.

170. A POSA would have been motivated to determine whether any GTIs were present in a cabozantinib (L)-malate composition. Tr. 301:8-24 (Lepore); 764:17–25 (Myerson).

171. A POSA would have known that the 1-1 impurity is the starting material used in Brown Example 1. DTX-291.25 (Scheme 1); Tr. 300:8–21 (Lepore); 676:25-677:2 (MacMillan).

172. Because FDA GTI Guidance "applies to known starting materials," a POSA would have assessed whether the 1-1 is a GTI. DTX-091.4; Tr. 301:18–302:7 (Lepore).

173. A POSA "would look at the structure for the 1-1 impurity" and know that it is

"potentially genotoxic because it's a quinoline." Tr. 771:17–20, 769:16–770:4 (Myerson); 303:5–306:16 (Lepore).

174. A POSA would have known that quinoline and quinoline analogs—including an analog structurally similar to the 1-1 impurity sharing the same substituent—were known to be genotoxic (DTX-313.4; Tr. 305:14–306:3 (Lepore)); which "would have set off a red flag" when assessing the 1-1 impurity for genotoxicity. Tr. 303:21–304:13, 306:5–11 (Lepore).

175. Following FDA GTI Guidance, requiring that impurities with structural alerts be further evaluated by an Ames test, a POSA would have determined that the 1-1 was a GTI. DTX-091.9; Tr. 303:5–15, 306:12–16 (Lepore), 771:17–25 (Myerson).

2. FDA Guidance requiring the industry to control GTIs would have motivated a POSA to limit the 1-1 impurity to low PPM levels.

176. Because FDA GTI Guidance's acceptable exposure levels would have required the 1-1 impurity at a level below 50 ppm, a POSA would have been motivated to reduce the impurity to those levels to allow it to be used in a clinical trial. DTX-091.13–.14; Tr. 307:9–19 (Lepore).

3. FDA Guidance would have motivated a POSA to use recrystallization as a GTI control strategy with a reasonable expectation of success.

177. If the cabozantinib (L)-malate from Brown Example 1 were not essentially free of the 1-1 impurity, it would not have complied with FDA GTI Guidance, and thus, the "first thing" a POSA would have attempted is a recrystallization. Tr. 307:23–308:9 (Lepore).

178. Because FDA guidances (DTX-091.4 and DTX-304.43) recommended recrystallization as an approach to "maximize the removal of the relevant impurity," a POSA would have been motivated to use recrystallization as a purification route to remove the 1-1 impurity with a reasonable expectation of success. DTX-091.4; Tr. 309:7–310:3 (Lepore).

179. A POSA would have been motivated to use recrystallization to remove the 1-1 impurity with a reasonable expectation of success because many prior-art examples showed that

recrystallization successfully purifies an API of an impurity, including removing GTIs down to less than 1 ppm. DTX-328.9; DTX-251.4; Tr. 310:11–311:3 (Lepore).

180. Dr. Myerson admitted that a POSA would have been interested in using recrystallization to remove GTIs. Tr. 793:19–24 (Myerson).

181. Dr. MacMillan admitted that a POSA would have reasonably expected that crystallization would reduce the 1-1 impurity in Brown Example 1. Tr. 679:6–22 (MacMillan).

182. Recrystallization successfully minimizes the level of the 1-1 impurity in cabozantinib (L)-malate. PTX-35.12 ("A recrystallization step was introduced in order to minimize the levels of GTIs."); Tr. 572:2–572:21 (Wilson).

C. A POSA would have found it obvious to formulate cabozantinib (L)-malate into a tablet or capsule.

183. A POSA would have been motivated to formulate the claimed compositions with a reasonable expectation of success. Tr. 397:17–398:23, 409:14–19 (Donovan).

1. A POSA would have been motivated to formulate cabozantinib (L)-malate into a tablet or capsule comprising a filler, disintegrant, glidant, and lubricant.

184. A POSA would have been motivated by Brown's disclosure that the "particularly preferred" dosage form for cabozantinib (L)-malate is a capsule or tablet for oral administration. DTX-291.22 ¶ 87; Tr. 390:25–391:8 (Donovan).

185. Brown's disclosure—that cabozantinib (L)-malate may be formulated by methods known in the art (e.g., Remington's) by mixing with fillers, disintegrants, lubricants, and glidants such as talc—would have motivated a POSA to formulate the pharmaceutical composition of claim 3 of the '349 patent. DTX-291.21 ¶ 82; Tr. 394:1–13 (Donovan).

186. Lachman's disclosure of drug-agnostic prototype formulations including the claimed excipients, which "would likely be successful" when used with cabozantinib (L)-malate,

would have further motivated a POSA. Tr. 379:13–380:19, 392:22–394:8, 421:2–6 (Donovan).

187. The '081 Application's disclosure that TKIs can be formulated into tablets and capsules comprising fillers, disintegrants, lubricants, and glidants would have further motivated a POSA. DTX-335.14–.15; Tr. 381:16–382:23, 394:1–13 (Donovan).

2. A POSA would have had a reasonable expectation of success at formulating a tablet or capsule that is essentially free of the 1-1 impurity.

188. During formulation development, a POSA would have known to monitor and control for the 1-1 impurity because it would have already been identified as a GTI during the API development. Tr. 397:6–16 (Donovan), 766:13-24; 772:1-3 (Myerson), 975:13–16 (George admitting that "in formulating a drug product, a research team [would have been] motivated to avoid or minimize genotoxic impurities as much as possible").

189. A POSA would have monitored for the 1-1 impurity during formulation activities to ensure that no toxic substances were formed. DTX-288.63; Tr. 385:1–7, 413:2–10 (Donovan).

190. As required by the FDA, it would have been routine for a POSA using known analytical techniques to determine whether the 1-1 impurity forms during "the manufacture or storage" of the drug product. Tr. 759:16–760:25: 763:6–16 (Myerson).

191. As part of routine formulation development, a POSA would have determined whether conditions such as heat and water or whether interactions with excipients could cause formation of the 1-1 impurity. Tr. 761:11–24, 762:10–23 (Myerson).

192. A POSA would have understood that cabozantinib (L)-malate is a "very stable compound" and "it would not be expected that the 1-1 impurity would form as a degradation product." Tr. 661:15–18, 663:8–11 (MacMillan), 722:7–10 (Myerson).

193. "Other than [the] synthetic process that makes [cabozantinib (L)-malate] API," the '349 patent does not disclose "anything additional that would control for the 1-1." Tr. 773:7–13

(Myerson). The "key feature" to "reliably manufacture" a cabozantinib (L)-malate tablet or capsule is the ability to obtain API with low levels of the 1-1 impurity. Tr. 697:25–698:7, 702:8–13 (Myerson); *see also id.* 617:3–14 (Shah), 399:18–400:19 (Donovan).

194. The claimed formulations "can be easily formulated" "according to methods available to the skilled artisan." JTX-4.14, at 21:37–45; Tr. 401:15–23 (Donovan), 777:12–15 (Myerson admitting that it is up to the POSA to perform formulation "tasks" of the '349 patent).

195. The '349 patent states that "known techniques for [] bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions [of claim 3 of the '349 patent] and are described in [the prior-art references Remington's and Swarbrick]." JTX-4.13, at 20:36–52; Tr. 401:7–13 (Donovan).

196. Selecting a specific filler, disintegrant, glidant, and lubricant and their relative concentrations is within the skill of a POSA. Tr. 748:3–17 (Myerson), 380:16–19 (Donovan).

VII. NO OBJECTIVE INDICIA SUPPORT NONOBVIOUSNESS FOR THE MALATE SALT PATENTS OR THE '349 PATENT

A. Exelixis failed to demonstrate any nexus to the asserted patents.

197. Dr. Myerson testified that "the nexus between the '349 patent and the objective indicia" relates to the '349 patent's disclosure of "a synthetic process to produce cabozantinib (L)-malate," but he admitted that the asserted claim 3 of the '349 patent is not directed to a synthetic process. Tr. 740:22–741:5, 745:6–16 (Myerson).

198. An equally viable formulation of cabozantinib (L)-malate could be formulated that is essentially free of the 1-1 impurity but that is not covered by the scope of claim 3 of the '349 patent, such as a formulation that does not contain a glidant. Tr. 404:6–19 (Donovan).

199. In the Cabozantinib I Case, *Exelixis, Inc. v. MSN Lab'ys Priv. Ltd.*, No. CV 19-2017-RGA-SRF (D. Del.), Mr. Tate testified that the commercial success of Cabometyx was

attributable to claim 5 of the ’473 patent. Tr. 987:22–988:19, 985:21–986:18 (Tate).

200. Mr. Tate provided “exactly the same” analysis of commercial success in this case as he did in the Cabozantinib I Case, which demonstrates that he failed to properly evaluate nexus. Tr. 1021:3–9, 1019:13–25 (McDuff).

201. Mr. Tate failed to weigh the patents asserted in this case against the other Exelixis patents listed in the Orange Book in analyzing nexus. Tr. 1019:18–25, 1017:17–24 (McDuff).

B. The existence of a blocking patent discounts any alleged objective indicia of long-felt, unmet need and commercial success.

202. MSN’s experts offered unrebutted testimony that the ’473 patent (DTX-013), and its parent application, the ’140 Publication (DTX-192), whose claims cover the use of cabozantinib, acted as a blocking patent for entities other than Exelixis that wanted to develop treatments for and/or pursue commercialization of cabozantinib. Tr. 402:21–404:1 (Donovan), 485:23–487:2 (Steed), 1014:17–1015:2 (McDuff).

203. MSN’s experts testified that the blocking period began in August 2005 with the publication of the ’140 Publication and extends through the patent term of the ’473 patent. Tr. 403:9–404:1 (Donovan), 485:23–487:2 (Steed), 1016:12–14 (McDuff). A POSA would be discouraged from developing technology covered by the ’140 Publication because the application could be granted and the POSA would then infringe those claims. Tr. 486:20–487:2 (Steed).

204. There was no development by others during the blocking period leading up to the 2009 and 2011 priority dates of the Malate Salt Patents and the ’349 patent. Tr. 1018:12–13 (McDuff). The risk that Exelixis would have altogether refused to grant a license to another entity was high, because Exelixis had announced exclusive collaborations with GSK and BMS. Tr. 1018:20–22 (McDuff). The economic opportunity for another entity pursuing cabozantinib would have been low in light of strong blocking disincentives. Tr. 1018:23–24 (McDuff).

205. Even if sales of Cabometyx and Cometriq were successful, no inference can be made based on those sales about whether the Malate Salt Patents or the '349 patent would have been obvious because of the "strong deterrence." Tr. 1016:23–1017:7, 1018:1–1019:7 (McDuff).

C. Exelixis has not shown the satisfaction of a long-felt, unmet need.

206. TKIs block tyrosine kinases that can lead to cancer. Tr. 993:1–3 (Mega).

207. Imatinib (Gleevac), which was the first approved TKI in 2001, "represented a really profound advancement," providing "extraordinary" efficacy and a better side-effect profile than previous cancer treatments. Tr. 993:10–994:10 (Mega).

208. By 2009, eight other TKIs had been approved and demonstrated clinical efficacy in treating kidney cancer, lung cancer, breast cancer, or chronic leukemia: imatinib, gefitinib, erlotinib, sorafenib, sunitinib, dasatinib, nilotinib, and pazopanib. Tr. 962:18–963:21 (George), 994:11–17 (Mega); DDX(Mega)-3.

209. Six of the eight TKIs available by 2009 were known to be "spectrum-selective," which refers to simultaneous inhibition of multiple kinases, and had overlapping TKI targets with cabozantinib. Tr. 963:22–964:25 (George), 994:11–995:4 (Mega). While TKI pathways are distinct, they often merge into more prominent pathways that influence cellular proliferation and growth, "similar to secondary roads leading into interstate highways." Tr. 995:8–13 (Mega).

210. Cabozantinib is an anti-VEGFR TKI, but use of anti-VEGFR TKIs was already the standard of care for RCC therapy in 2009, and prior-art anti-VEGFR TKIs included sunitinib, sorafenib, and pazopanib. Tr. 965:1–15 (George), 996:16–21 (Mega).

211. The NCCN guidelines recommend preferred regimens other than cabozantinib for first-line RCC treatment and recommend regimens other than cabozantinib for subsequent-line RCC treatment. PTX-528.15–-16; Tr. 966:6–967:24 (George), 998:10–16, 1002:13-7 (Mega).

212. The standard of care for RCC treatment today is combination therapy with a TKI

and an immune checkpoint inhibitor. Tr. 998:25–999:5 (Mega). The immune checkpoint inhibitor aspect has been instrumental in improving patient outcomes. Tr. 970:18–971:3 (George).

213. Like other TKIs, cabozantinib has a similar toxicity profile, and most RCC patients develop a resistance to it. Tr. 971:24–972:3 (George), 1004:23–1005:2 (Mega).

214. Dr. George testified that any drug that extended the lives of patients beyond previously available therapies meets a long-felt, unmet need. Tr. 961:23–962:2 (George).

215. Cabozantinib provided incremental improvement in therapy representing a difference in degree, not a difference in kind. Tr. 996:8–11, 1005:18–1006:1 (Mega).

216. An unmet need still exists today to improve RCC treatment on both the front line and subsequent line treatments for RCC. Tr. 962:13–16 (George), 1004:14–22 (Mega).

D. Exelixis has not shown commercial success.

217. Mr. Tate's analysis lacked any "definition of success," meaning that Exelixis failed to provide a basis of comparison to know whether Cabometyx sales and prescriptions were high, low, or somewhere in between. Tr. 1022:23–1023:8 (McDuff).

218. Mr. Tate's analysis failed to evaluate development and commercialization costs necessary to bring the product to market and failed to evaluate a return on investment to determine whether the product is successful. Tr. 1023:17–1024:2 (McDuff).

219. Mr. Tate's analysis was incomplete because it provided a "wide range of market shares" with no guidance on whether Cabometyx's market share is high or low, and whether the product is a commercial success. Tr. 1024:3–15 (McDuff).

E. Exelixis has not shown that the crystalline (L)-malate salt of cabozantinib produced unexpected results.

220. It was not "unexpected" for the (L)-malate salt of cabozantinib to be the preferred salt for development, because for a result to be unexpected, there would first need to be an

expectation that it would not work. Tr. 484:16–485:19 (Steed). Through a routine salt screen, a POSA would have selected acids and put them through the process, and there would not be an expectation that a given acid would not work. Tr. 484:22–485:4 (Steed), 828:3–12 (Koleng).

221. The solubility of crystalline cabozantinib (L)-malate was not unexpected. Tr. 485:5–19 (Steed). Rather, amorphous cabozantinib (L)-malate behaves unexpectedly, because it dissolves anomalously slowly and forms clumps. Tr. 485:12–19 (Steed).

222. Dr. Shah, and Exelixis, concluded in 2014 that amorphous material of XL184 [cabozantinib] in contact with aqueous media tended to form gel-like clumps that do not disburse and are very slow to dissolve, and that "chunks of undissolved material (gel-like lumps) were found in the amorphous material." Tr. 640:18–641:6 (Shah); PTX-161.4, 8.

223. Dr. Shah's sworn declaration to the Patent Office regarding dissolution results did not characterize the results as "unexpected" or "surprising." PTX-225.

F. Exelixis has not shown that the compositions of claim 3 of the '349 patent produced unexpected results.

224. A POSA would not have expected degradation of cabozantinib (L)-malate to form the 1-1 impurity. Tr. 661:1–18; 6638-11 (MacMillan).

225. A POSA would have expected that cabozantinib (L)-malate that is essentially free of the 1-1 impurity could be formulated into a capsule or tablet that is essentially free of the 1-1 impurity. Tr. 399:18–400:19 (Donovan). That capsules essentially free of the 1-1 impurity were manufactured using the Regis Batches shows that it was expected that cabozantinib (L)-malate could be formulated into a capsule essentially free of the 1-1 impurity. Tr. 400:2–8 (Donovan).

226. A POSA would have expected that wet granulation could be used to formulate a cabozantinib (L)-malate tablet essentially free of the 1-1 impurity. Tr. 400:11–19 (Donovan).

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